METHODS OF USING ANTI-CGRP ANTAGONIST ANTIBODIES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional application of U.S. patent application Ser. No. 12/093,638, filed May 14, 2008, issued as U.S. Pat. No. 8,007,794, on Aug. 30, 2011, which is a national stage of PCT International Application No. PCT/IB2006/003181, filed Nov. 2, 2006, which claim priority to U.S. Provisional Patent Application No. 60/736,623, filed Nov. 14, 2005, all of which are incorporated herein in their entireties by reference.

FIELD OF THE INVENTION

The present invention relates to the use of anti-CGRP antagonist antibodies for the prevention, amelioration, or treatment of vasomotor symptoms, such as CGRP related headaches (e.g., migraine) and hot flushes.

BACKGROUND OF THE INVENTION

CGRP (calcitonin gene-related peptide) is a 37 amino acid neuropeptide, which belongs to a family of peptides that includes calcitonin, adrenomedullin and amylin. In humans, two forms of CGRP (α-CGRP and β-CGRP) exist and have similar activities. They vary by three amino acids and exhibit differential distribution. At least two CGRP receptor subtypes may also account for differential activities. CGRP is a neurotransmitter in the central nervous system, and has been shown to be a potent vasodilator in the periphery, where CGRP-containing neurons are closely associated with blood vessels. CGRP-mediated vasodilatation is also associated with neurogenic inflammation, as part of a cascade of events that results in extravasation of plasma and vasodilation of the microvasculature and is present in migraine.

CGRP has been noted for its possible connection to vasomotor symptoms (Wyon et al. Scand. J. Urol. Nephrol. 35: 92-96 (2001); Wyon et al. Menopause 7(1):25-30 (2000)). Vasomotor symptoms (VMS), such as hot flushes and night sweats, are the most common symptoms associated with menopause, occurring in 60% to 80% of all women following natural or surgically-induced menopause. Hot flushes are likely to be an adaptive response of the central nervous system (CNS) to declining sex steroids (Freedman Am. J. Human Biol. 13:453-464 (2001)). To date, the most effective therapies for flushes are hormone-based treatments, including estrogens and/or some progestins. Hormonal treatments can be effective for alleviating flushes, but are not appropriate for all women. Psychological and emotional symptoms observed, such as nervousness, fatigue, irritability, insomnia, depression, memory loss, headache, anxiety, nervousness or inability to concentrate are considered to be caused by the sleep deprivation following hot flush and night sweats (Kramer et al., In: Murphy et al., 3.sup.rd Symposium on Recent Advances in Urological Cancer Diagnosis and Treatment-Proceedings, Paris, France: SCI: 3-7 (1992)).

Men also experience hot flushes following steroid hormone (androgen) withdrawal. This is true in cases of age-associated androgen decline (Katovich, et al., Proceedings of the Society for Experimental Biology & Medicine, 1990, 193(2): 129-35) as well as in extreme cases of hormone deprivation associated with treatments for prostate cancer (Berendsen, et al., European Journal of Pharmacology, 2001, 419(1): 47-54). As many as one-third of these patients will

experience persistent and frequent symptoms severe enough to cause significant discomfort and inconvenience.

CGRP is a potent vasodilator that has been implicated in the pathology of other vasomotor symptoms, such as all forms of vascular headache, including migraines (with or without aura) and cluster headache. Durham, N. Engl. J. Med. 350:1073-1075, 2004. The serum levels of CGRP in the external jugular vein are elevated in patients during migraine headache. Goadsby et al., Ann. Neurol. 28:183-7, 1990. Intravenous administration of human α-CGRP induced headache and migraine in patients suffering from migraine without aura, suggesting that CGRP has a causative role in migraine. Lassen et al., Cephalalgia 22:54-61, 2002.

Possible CGRP involvement in migraine has been the basis for the development and testing of a number of compounds that inhibit release of CGRP (e.g., sumatriptan), antagonize at the CGRP receptor (e.g., dipeptide derivative BIBN4096BS (Boerhringer Ingelheim); CGRP (8-37)), or interact with one or more of receptor-associated proteins, such as, receptor activity membrane protein (RAMP) or receptor component protein (RCP), both of which affect binding of CGRP to its receptors. Brain, S. et al., Trends in Pharmacological Sciences 23:51-53, 2002. Alpha-2 adrenoceptor subtypes and adenosine A1 receptors also control (inhibit) CGRP release and trigeminal activation (Goadsby et al., Brain 125:1392-401, 2002). The adenosine A1 receptor agonist GR79236 (metrafadil), which has been shown to inhibit neurogenic vasodilation and trigeminal nociception in humans, may also have anti-migraine activity (Arulmani et al., Cephalalgia 25:1082-1090, 2005; Giffin et al., Cephalalgia 23:287-292, 2003.)

Confounding this theory is the observation that treatment with compounds that exclusively inhibit neurogenic inflammation (e.g., tachykinin NK1 receptor antagonists) or trigeminal activation (e.g., $5HT_{1D}$ receptor agonists) have been shown to be relatively ineffective as acute treatments for migraine, leading some investigators to question whether inhibiting release of CGRP is the primary mechanism of action of effective anti-migraine treatments. Arulmani et al., Eur. J. Pharmacol. 500:315-330, 2004.

Migraine is a complex, common neurological condition that is characterized by severe, episodic attacks of headache and associated features, which may include nausea, vomiting, sensitivity to light, sound or movement. In some patients, the headache is preceded or accompanied by an aura. The headache pain may be severe and may also be unilateral in certain patients.

Migraine attacks are disruptive to daily life. In US and Western Europe, the overall prevalence of migraine sufferers is 11% of the general population (6% males; 15-18% females). Furthermore, the median frequency of attacks in an individual is 1.5/month. While there are a number of treatments available to alleviate or reduce symptoms, preventive therapy is recommended for those patients having more than 3-4 attacks of migraine per month. Goadsby et al. New Engl. J. Med. 346(4): 257-275, 2002.

The variety of pharmacologic interventions that have been used to treat migraine and the variability in responses among patients are a testament to the diverse nature of this disorder. Thus, such relatively non-selective drugs as ergot alkaloids (e.g., ergotamine, dihydroergotamine, methysergide), which exhibit serotonergic, as well as adrenergic, noradrenergic and dopaminergic activity, have been used for over eighty years to treat migraine. Other treatments include opiates (e.g., oxycodone) and β-adrenergic antagonists (e.g., propranolol). Some patients, usually those with milder symptoms, are able to control their symptoms with non-prescription remedies